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Health and Environmental Effects Profile for Monochlorobutanes

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MONOCHLOROBUTANES

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The Health and Environmental Effects Profile for Monochlorobutanes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Monochlorobutanes.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

		page
	EXECUTIVE SUMMARY	vi
1.	INTRODUCTION.	-1-
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES.	-3-
3.	EXPOSURE.	-8-
4.	PHARMACOKINETICS.	-9-
5.	EFFECTS	-10-
6.	AQUATIC TOXICITY.	-19-
7.	EXISTING GUIDELINES AND STANDARDS	-20-
8.	APPROACHES TO RISK ASSESSMENT	-21-
9.	REFERENCES.	-22-

EXECUTIVE SUMMARY

Chlorobutanes are highly flammable, volatile liquids used as solvents and alkylating agents in organic synthesis. They range from moderately to slightly soluble in water. Information on the environmental fate of these compounds is sparse, but neither photolysis nor oxidation appear to be important processes while hydrolysis rates for various isomers range from slow for 1-chlorobutane to fast for 2-chloro-2-methylpropane (t-butyl chloride). No monitoring data were available to allow evaluation of human exposure to these chemicals.

Limited information is available on the toxicity of the monochlorobutanes in animals, and no data were found on effects in humans. Acute lethal studies with 1- and 2-chlorobutane in rats indicate a low order of acute toxicity following oral and inhalation exposure, and the results of pathologic examinations of dogs following oral administration of single nonlethal doses of these compounds suggest that the liver and kidney are primary target organs. Low acute dermal toxicity is also indicated by high LD_{50} values (>17 g/kg) and mild (1-chlorobutane) to no (2-chlorobutane) primary skin irritation following application of single doses to the skin of rabbits. Application of these compounds onto the cornea of rabbits caused mild necrosis. Information was not found on the effects of acute exposure to t-butyl chloride.

Limited data on the effects of subchronic exposure to 1-chlorobutane are available from abstracts of Russian studies; daily oral exposure for 30 or 60 days reportedly caused autosensitization (0.0022-110 mg/kg/day) and alterations in blood chemistry values (2 mg/kg/day), respectively, in rats.

Chronic toxicity studies with the monochlorobutanes have not been performed. 1-Chlorobutane, 2-chlorobutane and t-butyl chloride have been tested for carcinogenic activity in the Strain A mouse lung tumor system. Increases in the number of pulmonary adenomas per mouse were associated with administration of several doses of 2-chlorobutane and t-butyl chloride, but significant dose response relationships were not demonstrated, and the positive results observed in this assay may be regarded only as suggestive of carcinogenic activity. A carcinogenicity bioassay of orally administered 1-chlorobutane is currently being conducted in rats and mice by the National Toxicology Program. 1-Chlorobutane has recently been reported to be non-mutagenic to Salmonella typhimurium with or without metabolic activation in two well-designed Ames assays. It was noted in an abstract of another Russian study that oral administration of 1-chlorobutane during pregnancy caused embryotoxic and teratogenic effects in rats, but details regarding the design or results of this study were not available.

Limited information was found on the aquatic toxicity of 1-chlorobutane. A 7-day LC_{50} value of 97 mg/ℓ has been reported for the guppy, Poecilia reticulata. A calculated bioconcentration factor (BCF) of 36 indicates that 1-chlorobutane has a low potential for bioaccumulation.

1. INTRODUCTION

1-Chlorobutane (n-butyl chloride) is a highly flammable liquid with a pungent odor (Verschueren, 1977). The compound is prepared from n-butyl alcohol by heating with HCl and anhydrous $ZnCl_2$. Some physical parameters are:

CAS registry number	109-69-3
Formula	$CH_3CH_2CH_2CH_2Cl$
Molecular weight	92.57
Melting point	-123.1°C (Weast, 1980)
Boiling point	78.4°C (Weast, 1980)
Density (g/mℓ) at 20/4°C	0.8862 (Weast, 1980)
Flash point	-6.7°C (Windholz, 1976)
Vapor pressure	80.1 mm at 20°C (Verschueren, 1977)
Solubility in water	660 mg/ℓ at 12°C (Windholz, 1976) ≈780 mg/ℓ at 25°C (Mabey et al., 1982)
Log octanol/water partition coefficient (calculated)	≈2.57 (Mabey et al., 1982) ≈2.35 (Könemann, 1981)

In the United States, 1-chlorobutane is produced by Beckman Institute, Inc., Palo Alto, California; Publicker Chemical Corp., Greenwich, Connecticut; and Union Carbide Corp., Institute, West Virginia (SRI, 1981). It is used as a butylating agent in organic synthesis, namely in the manufacture of butyl cellulose and in veterinary medicine for the removal of intestinal nematodes in dogs (Windholz, 1976).

2-Chlorobutane (sec-butyl chloride) is a liquid at ambient temperature and has a pleasant, ethereal odor (Windholz, 1976). It is prepared from sec-butyl alcohol, HCl and $ZnCl_2$ (Windholz, 1976). This compound has been detected in turbine combustion exhaust (Graedel, 1978). Some physical paramters are:

CAS registry number	78-86-4
Formula	$CH_3CH_2CHClCH_3$
Molecular weight	92.57
Melting point	-131.3°C (Weast, 1980)
Boiling point	68.2°C (Weast, 1980)
Density (g/mℓ) at 20/4°C	0.8732 (Weast, 1980)
Vapor pressure	126.7 mm at 20°C (Roland, 1928)
Solubility in water	1000 mg/ℓ at 25°C (Windholz, 1976)
Log octanol/water partition coefficient (calculated)	2.44 (Mabey et al., 1982)

In the U.S., the chemical is produced by Filo Chemical Corp., New York, New York and Wall Chemical Corp., Westfield, New Jersey (CMR, 1981). It is used in organic synthesis (Hawley, 1977).

2-Chloro-2-methyl propane (t-butyl chloride) is prepared by shaking t-butyl alcohol with concentrated HCl and then distilling (Windholz, 1976). Some physical parameters are:

CAS registry number	507-20-0
Formula	$(CH_3)_3$ CCl
Molecular weight	92.57
Melting point	-25.4°C (Weast, 1980)
Boiling point	51°C (Windholz, 1976)
Density (g/mℓ) at 20/4°C	0.8420 (Weast, 1980)
Vapor pressure	301 mm at 25°C (Weast, 1973)
Solubility in water (calculated)	1500 mg/ℓ (Mabey et al., 1982)
Log octanol/water partition coefficient (calculated)	2.31 (Mabey et al., 1982)

In the United States, the chemical is produced by Columbia Organic Chemical Co., Inc., Columbia, South Carolina and Guardian Chemical Corp., Hauppauge, New York (SRI, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Pertinent experimental data regarding environmental fate and transport processes of monochlorobutanes in air were not located in the available literature. However, Mabey et al. (1982) give information on vapor pressure and water solubility for 1-chlorobutane which conveys information on the tendency to move from other environmental media to air. The same authors also render a professional judgment that photolysis is not anticipated to be environmentally relevant. This usually signifies the molecule is not anticipated to undergo direct photolysis because it does not absorb solar radiation energetic enough to break chemical bonds existing in the molecule, i.e., slightly longer than the short wavelength cutoff (290-300 mm) imposed by atmospheric absorption. (Still longer wavelength absorption undoubtedly occurs, but results only in exitation of various vibrational modes in the intact molecule.) Questions of indirect photolysis, involving reaction with other photolytically activated molecules or radicals, or other reactions with more reactive atmospheric chemical species are not addressed direct in Mabey et al. (1982).

2.2. WATER

Some theoretical predictions about the transport of 1-chlorobutane in aquatic media can be made. Based on the vapor pressure and solubility data, (estimated 700 mg/ℓ at 20°C), the Henry's law constant for this compound can be estimated to be 1.39×10^{-2} atm. m^3/mol. Thus, the Henry's law constant for 1-chlorobutane is close to that of cumene (1.46×10^{-2} atm. m^3/mol) (Mackay and Leinonen, 1975). Mackay and Leinonen (1975) estimated the half-life of evaporation for cumene from a water depth of 1 m to be ≈6 hours. If the mass transfer coefficient of 1-chlorobutane in aquatic media

is assumed to be the same as that of cumene, the evaporation half-life of 1-chlorobutane from aquatic media can be predicted to exceed 6 hours. In situations where the water body is turbulent, the liquid phase mass transfer coefficient may be considerably higher, and the evaporation rate may increase proportionally (Mackay and Leinonen, 1975).

The sediment sorption partition coefficient for 1-chlorobutane from aquatic media can be estimated from physical properties of the molecule. The organic carbon partition coefficient (K_{oc}) is first calculated from the octanol-water partition coefficient (K_{ow}) by correlation equations. The sediment sorption partition coefficient is then calculated from K_{oc} by the relation:

$$\text{Sorption partition coefficient} = \frac{K_{oc} \times \% \text{ organic carbon content}}{100\%}$$

Using values of 2.35 and 2.57 for log K_{ow} (Könemann, 1981; Mabey et al., 1982), log K_{oc} is calculated to be within the range 2.10-2.78, depending on the correlation equation used (Briggs, 1981; Schwarzenbach and Westall, 1981; Kenaga and Goring, 1980). This log k_{oc} value is close to the experimental log k_{oc} value of 2.60 for tetrachloroethylene (Schwarzenbach and Westall, 1981). Thus, the sorption characteristic of 1-chlorobutane in aquatic media can be expected to be similar to that of tetrachloroethylene. It has been reported by Callahan et al. (1979) that tetrachloroethylene is not significantly sorbed to sediments containing low organic matter, whereas sediments rich in organic matter may show higher sorption capacity. If a sediment organic content of 0.5% (typical of river sediment) is assumed, a sediment sorption partition coefficient of 0.63-2.98 is estimated, indicating a sediment concentration roughly equivalent to the water concentration under equilibrium conditions.

The hydrolysis of 1-chlorobutane in water was studied by Koskikallio (1967). From the rate constant given in this study, the hydrolysis half-life of 1-chlorobutane in water at 40°C was determined to be 59 days. An estimate by Mabey et al. (1982) of the rate constant for neutral hydrolysis of 1-chlorobutane and 2-chlorobutane at 25°C as equal to 8×10^{-4} $hour^{-1}$ at 25°C is in apparent disagreement with the above.* The half-life for each would thus be 36 days, rather than the 60+ days anticipated based on the work of Koskikallio (1967) at a higher temperature. This discrepancy has not been resolved but in the absence of other degradation mechanisms such as oxidation (Mabey et al., 1982) or photolysis (after partitioning to the atmosphere), even slow hydrolysis may remain a significant fate process. The environmental fate of 2-chloro-2-methylpropane is relatively straightforward compared to the complex situation with 1-chlorobutane and 2-chlorobutane. The hydrolysis half-life for t-butyl chloride was determined to be 13 minutes at 1°C (Koskikallio, 1967), 8 minutes at 4°C (Laughton and Robertson, 1959), and 23 seconds at 25°C (Mabey and Mill, 1978). Thus, it appears that hydrolysis of t-butyl chloride would be the primary mode of transformation of the compound in the aqueous phase.

The biodegradation of 1-chlorobutane by isolated microorganisms was studied by Buswell and Jurtschuk (1969) and Marion and Malaney (1963). Buswell and Jurtschuk (1969) isolated resting cell suspensions of Corynebacterium sp. from soil and incubated the microorganisms in the presence of 1-chlorobutane under an optimum condition of pH (7.0-7.6) and temperature

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*Mabey et al. (1982) caution that their estimated rate constants and calculated physical parameters were intended only for determining the relative contributions of potential degradation or dissipation mechanisms and should not be used to determine absolute rates without further consultation with the authors.

(30°C). These investigators found that only 31.4 µℓ of O_2 were consumed per hour/mg dry cell weight for 1-chlorobutane, compared to 78.5 µℓ of O_2 for n-octane. Marion and Malaney (1963) isolated Alcaligenes faecalis from activated sludge, and determined that 1-chlorobutane was relatively resistant to oxidation by this species of microorganisms. The relevance of such studies that utilize isolated microorganisms to evaluate the biodegradation potential of a chemical under natural aquatic conditions is questionable at best.

The biodegradability of 1-chlorobutane with activated sludge was studied by Gerhold and Malaney (1966). It was determined by these investigators that the percent of theoretical oxygen demand for 1-chlorobutane under the experimental conditions was as follows: 0.9% in 6 hours, 1.3% in 12 hours and 2.6% in 24 hours. In other words, 1-chlorobutane was not significantly oxidized by the sludge systems. Assuming a microbial degradation rate constant of 3×10^{-9} mℓ $cell^{-1}$ $hour^{-1}$ (Mabey et al., 1982) and the concentration of microorganisms in aquatic phase as 5×10^{5} cells $mℓ^{-1}$ (Burns et al., 1981), the biodegradation half-life for 1-chlorobutane in aquatic media can be calculated to be ≈19 days. Therefore, biodegradation may not be a significant fate process for this compound.

2.3. SOIL AND OTHER MEDIA

The fate and transport of 1-chlorobutane in soil is difficult to predict from the available data. Based on the similarity of the log k_{oc} value of this compound and tetrachloroethylene, the leaching and volatility of 1-chlorobutane from soil can be expected to be similar to that of tetrachloroethylene. Predictions regarding the microbial degradability and chemical oxidation ability of this compound in soil are difficult to make at the present time.

2.4. SUMMARY

It should be emphasized that the fate of a chemical predicted from theoretical calculations may vary considerably from the experimental data. In the preceding discussions, the fate of 1-chlorobutane due to a few likely environmental processes has been predicted from theoretical equations only when experimental data were not available. However, extreme caution should be exercised when interpreting the predicted fate data based on theoretical calculations or estimations. Experimental data are virtually always preferred and should be substituted in prediction schemes at the earliest opportunity.

3. EXPOSURE

Few monitoring data were found for the three compounds in any media. Williams (1965) detected 2-chlorobutane in the air of Vancouver, British Columbia, Canada, but the amount was not quantified. The odor threshold of 1-chlorobutane in reservoir water was determined to be 0.4-0.8 mg/ℓ (Rudnev et al., 1979).

4. PHARMACOKINETICS

4.1. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Pertinent data regarding the absorption, distritution, melabolism and excretion of monochlorobutane could not be located in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

1-Chlorobutane, 2-chlorobutane and t-butyl chloride have been tested for carcinogenic activity in the Strain A mouse lung tumor system (Poirier et al., 1975). A/He mice of both sexes, 6-8 weeks old, were injected intraperitoneally 3 times/week for a total of 24 (1-chlorobutane and t-butyl chloride) or 13 (2-chlorobutane) injections. Three dose levels were employed that represented the maximum tolerated dose and a 1:2 and 1:5 dilution of the maximum tolerated dose. Twenty mice were used at each dose level (10/sex), including negative (tricaprylin, saline) and positive (urethan) controls. Mice were sacrificed 24 weeks after the first injection, and the frequency of lung tumors in each test group was statistically compared with that in the vehicle-treated controls using Student's t-test and was not corrected for multiple testing.

The interpretation of lung tumor data in the Strain A mouse is somewhat unique in that certain specific criteria should be met before a compound is considered positive (Shimkin and Stoner, 1975):

(a) A significant increase in the mean number of lung tumors in test animals, preferably >1/mouse, should be obtained;

(b) A dose-response relationship should be evident;

(c) The mean number of lung tumors in control mice should be consistent with the anticipated incidence of spontaneous tumors for untreated Strain A mice.

The results obtained by Poirier et al. (1975) are summarized in Table 5-1. These data indicate that in no case were the first two criteria met, as indicated above, for the establishment of a positive response. Slight but statistically significant increases in the number of pulmonary adenomas/mouse were associated with administration of several of the doses of 2-chlo-

TABLE 5-1

Pulmonary Tumor Response of A/Ke Mice to Monochlorobutanes[a]

Compound	Vehicle	No. of i.p. Injections	Total Dose (mmol/kg)	No. of Animals (Survivors/Initial)	Percentage of Mice with Lung Tumors	Average No. of Lung Tumors/Mouse[b]	P
Untreated	NA	0	NA	29/30	20	0.21 ± 0.03	NA
Tricaprylin 1	NA	24	NA	154/160	22	0.22 ± 0.03	NA
Tricaprylin 2	NA	24	NA	14/15	36	0.36 ± 0.14	NA
0.85% NaCl solution	NA	24	NA	40/40	23	0.22 ± 0.02	NA
1-Chlorobutane	T-1[c]	24	65.0	19/20	32	0.31 ± 0.07	NS
	T-1	24	32.4	19/20	21	0.21 ± 0.05	NS
	T-1	24	12.9	19/20	16	0.15 ± 0.04	NS
2-Chlorobutane	T-3[d]	13[e]	35.0	10/20	80	1.20 ± 0.38	<0.05
	T-3	13	17.5	15/20	73	0.67 ± 0.22	NS
	T-3	13	7.0	15/20	40	0.53 ± 0.14	NS
t-Butyl chloride	T-3[d]	24	65.0	8/20	75	1.00 ± 0.27	<0.05
	T-3	24	32.4	11/20	55	0.73 ± 0.22	<0.05
	T-3	24	12.9	11/20	64	0.64 ± 0.15	NS
Urethan	NA	1	10 mg	19/20	100	8.1 ± 2.3	NA
	NA	1	20 mg	18/20	100	17.8 ± 4.32	NA

[a]Source: Poirier et al., 1975

[b]Mean ± S.E.; tumor data for males and females are combined

[c]Tricaprylin 1

[d]Tricaprylin 3

[e]13 instead of 24 injections were administered due to toxicity.

NA = Not applicable; NS = not specified; i.p. = intraperitoneal

robutane and t-butyl chloride, and the response to these compounds was somewhat elevated at the other dose levels used. Overall, the positive results of the 2-chlorobutane and t-butyl chloride experiments may be suggestive of carcinogenic activity, but do not in themselves provide an adequate basis for the development of a quantitative health risk assessment for humans. The negative results in the 1-chlorobutane assay cannot be regarded as unequivocal, because the results of recent validation studies with 60 known carcinogens have shown that a high percentage (50-90%) have false negative results (Maronpot, 1982).

The National Toxicology Program has begun a carcinogenicity bioassay of 1-chlorobutane in rats and mice (NTP, 1982); the chemical is being administered by gavage and testing for chronic toxicity is currently in progress.

5.2. MUTAGENICITY

1-Chlorobutane has recently been reported to be non-mutagenic to Salmonella typhimurium in modified Ames assays (Eder et al., 1980; Barber et al., 1981; Barber and Donish, 1982). The designs of these studies are noteworthy in that closed incubation systems were employed to prevent loss of compound due to volatilization. In the first study (Eder et al., 1980), strain TA100 was assayed in liquid suspension, both with and without rat liver homogenate fraction (S-9). Doses that ranged from 0.1-10 µl/2 ml incubation volume (=0.957-95.7 µmol) were employed (purity was 100%), and incubation tubes were tightly sealed with screw caps. The highest dose was reported to cause a survival rate of <10%. 1-Chlorobutane did not double the spontaneous background of revertants at any dose tested, and, therefore, was considered negative in this assay. In the Barber et al. (1981) study, tester strains TA1535, TA98 and TA100 were exposed to 1-chlorobutane vapor in a sealed containment system. 1-Chlorobutane was tested at concentrations that ranged

from 1.9-32.7 µmol/plate (the high dose produced observable toxicity), and assays were conducted with and without S-9 mix. 1-Chlorobutane did not increase the spontaneous background rate of any tester strain. Barber and Donish (1982) reported these same findings.

1-Chlorobutane and t-butyl chloride did not inhibit the growth of either DNA polymerase-deficient (P3478) or wild-type (P3110) E. coli in the pol A^- assay (Fluck et al., 1976). It should be noted that the lack of growth inhibition in both strains may be related to the facts that (1) apparently only single doses of the compounds were tested (0.24 µmol), (2) compound volatilization during incubation was apparently not controlled, and (3) metabolic activation was not employed.

5.3. TERATOGENICITY

It was noted in a recent Russian study (Rudnev et al., 1979) that oral administration of 1-chlorobutane has caused embryotoxic and teratogenic effects in rats. It appears that the compound was administered at a dose of 733 mg/kg on days 1 through 19 of pregnancy, but additional information regarding the design or results of this study were not presented.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of monochlorobutanes were not located in the available literature.

5.5. CHRONIC TOXICITY

Limited information is available on the effects of repeated oral exposure to 1-chlorobutane. The significance of the results reported in two studies summarized below is uncertain, however, due to a lack of detail regarding experimental design (strain, sex, number, vehicle, purity, duration of experiment) and responses.

It was noted that oral administration of 1-chlorobutane for 30 days at doses of 110 mg/kg/day (Rudnev et al., 1979) and 0.0022 mg/kg/day (Vinogradov, 1979) produced autosensitization in rats. The lower dose was reported to be a minimum autosensitizing dose (Vinogradov, 1979).

Daily oral administration of 1-chlorobutane to rats at a level of 2 mg/kg for 6 months reportedly raised the level of inorganic phosphate in the blood (Rudnev et al., 1979). "Altered" activity of blood alkaline, phosphatase, cholinesterase and succinic dehydrogenase was also observed.

5.6. ACUTE TOXICITY

Limited information is available on the acute toxic effects of 1- and 2-chlorobutane. As detailed in Table 5-2, most of the data on these compounds was generated in range-finding toxicity and irritation studies that were conducted by Smyth et al. (1954, 1969). No information was found regarding the acute toxicity of t-butyl chloride.

Single oral doses of 1- and 2-chlorobutane do not appear to be highly toxic, although the reported LD_{50}'s for 1-chlorobutane (≈2.2 and 2.7 g/kg) (Smyth et al., 1954; Rudnev et al., 1979) suggest that this compound is much more toxic (6-fold) than 2-chlorobutane (≈17.5 g/kg) (Smyth et al., 1969). A Russian study indicates that mice may be less sensitive to orally administered 1-chlorobutane (LD_{50} of 5.6 g/kg) than rats (Rudnev et al., 1979).

Wright and Schaffer (1932) evaluated the anthelmintic properties of a series of orally administered chlorinated alkyl hydrocarbons, including 1- and 2-chlorobutane, in dogs. In this study, 21 dogs were administered single doses of 1-chlorobutane, by gavage, that ranged from ≈0.09-8.86 g/kg (18 of 21 were given 0.09-0.27 g/kg), and 10 dogs were similarly dosed with ≈0.09-0.44 g/kg 2-chlorobutane (8 of 10 were given 0.17-0.26 g/kg).

TABLE 5-2

Acute Lethal and Irritant Effects of Monochlorobutanes

Compound	Route	Species/Strain	Sex	Number	Vehicle	Dosage	Response	Reference
1-Chlorobutane	oral (gavage)	rat/Carworth-Wistar	female	5/group	NS[a]	2.67 g/kg[b] (2.32-3.06)	Range-finding LD_{50} (14-day)	Smyth et al., 1954
	oral	rat/NS	NS	NS	NS[a]	2.2 g/kg	LD_{50}	Rudnev et al., 1979
	oral	mouse/NS	NS	NS	NS[a]	5.6 g/kg	LD_{50}	Rudnev et al., 1979
	inhalation	rat/NS	NS	6/group	NA	8000 ppm x 4 hours[c,d]	2 of 6 died within 14 days	Smyth et al., 1954
	inhalation	rat/albino	male	6/group	NA	concentrated vapor x 15 minutes[e,f]	Maximum time for 6 rats to survive 14 days	Smyth et al., 1954
	dermal	rabbit/New Zealand albino	male	4/group	NS[a]	>17.7 g/kg, single dose occluded 24-hour contact	Range-finding LD_{50} (14-day)	Smyth et al., 1954
	dermal	rabbit/albino	NS	5	undiluted	0.01 mL (8.86 mg), uncovered application	Strong capillary injection within 24 hours (Grade 3)	Smyth et al., 1954
	ocular	rabbit/albino	NS	5 eyes	undiluted	0.05 mL (44.3 mg), corneal application	Mild corneal necrosis (Grade 2) after 18-24 hours	Smyth et al., 1954

TABLE 5-2 (cont.)

Compound	Route	Species/Strain	Sex	Number	Vehicle	Dosage	Response	Reference
2-Chlorobutane	oral (gavage)	rat/Carworth-Wistar	male	5/group	NS[a]	17.46 g/kg[b] (11.18-27.33)	Range-finding LD_{50} (14-day)	Smyth et al., 1969
	inhalation	rat/NS	NS	6/group	NA	8000 ppm x 4 hours[c,d]	3 of 6 died within 14 days	Smyth et al., 1969
	inhalation	rat/albino	NS	6/group	NA	concentrated vapor x 5 minutes[e,f]	6 of 6 died within 14 days	Smyth et al., 1969
	dermal	rabbit/New Zealand albino	male	4/group	NS[a]	17.46 g/kg, single dose occluded 24-hour contact	Range-finding LD_{50} (14-day)	Smyth et al., 1969
	dermal	rabbit/albino	NS	5	undiluted	0.01 mℓ (8.73 mg), uncovered application to clipped skin	No irritation (Grade 1)	Smyth et al., 1969
	ocular	rabbit/albino	NS	5 eyes	undiluted	0.05 mℓ (43.7 mg), corneal instillation	Mild corneal necrosis (Grade 2)	Smyth et al., 1969

[a]Not specifically stated if the chemical was administered undiluted.

[b]Groups of 5 rats administered logarithmic series of doses that differed by a factor of 2.

[c]Nominal concentration

[d]Groups of 6 rats exposed to logarithmic series of concentrations that differed by a factor of 2.

[e]Rats were exposed to a flowing stream of air approaching saturation with monochlorobutane vapor; saturation concentration is ≈97,000 ppm.

[f]Groups of 6 rats exposed for a logarithmic series of time intervals that differed by a factor of 2.

NS = Not specified; NA = not applicable

Administration of 1-chlorobutane reportedly did not produce signs of overt toxicity or gross pathological lesions, but histological examination revealed cloudy swelling and passive congestion in the livers. Slight fatty infiltration in the renal collecting tubules and loops of Henle, and cloudy swellings in the tubular epithelium, were occasionally noted. It was suggested that 2-chlorobutane was more toxic than 1-chlorobutane, because exposure to the latter compound resulted in grossly observable pathologic changes (liver and kidney congestion, jaundice of the liver, hemorrhagic lesions of the gastrointestinal tract) and microscopic changes in the liver that were more pronounced. Kidney sections from the dogs that were exposed to 2-chlorobutane also showed passive congestion. It should be noted, however, that results of histological examinations were only presented for 7 of 21 dogs exposed to 1-chlorobutane, and 3 of 10 dogs exposed to 2-chlorobutane; it is not clear if tissues from all exposed dogs were examined. The validity of the conclusion that 2-chlorobutane is more toxic than 1-chlorobutane is therefore uncertain, because it is not known if it was based on a representative sampling of tissue sections.

Monochlorobutane vapor exposures indicate a low degree of inhalation toxicity in rats (see Table 5-2). Exposure to 1- or 2-chlorobutane at a concentration of 8000 ppm for 4 hours resulted in similar mortality after 14 days (2 of 6 and 3 of 6 died, respectively) (Smyth et al., 1954, 1969).

Dermal exposures to 1- and 2-chlorobutane also indicate a very low order of acute toxicity (Smyth et al., 1954, 1969); dermal LD_{50} values in rabbits were >17 g/kg for both of these compounds. Primary skin irritation studies suggested, however, that local reactions may be greater with 1-chlorobutane than with 2-chlorobutane (the compounds elicited mild irritation

and no irritation, respectively, 24 hours after uncovered application to clipped skin). Corneal application of undiluted 1- and 2-chlorobutane caused mild necrosis in rabbits (see Table 5-2).

5.7. OTHER RELEVANT INFORMATION

Hellman and Small (1974) characterized the odor properties of 101 petrochemicals, including 1-chlorobutane, using subjective responses of humans. The detection and recognition thresholds for 1-chlorobutane in air were determined to be 8.8 and 13.3 ppm, respectively.

The odor threshold concentration of 1-chlorobutane in water was reported in a Russian study to range from 106-211 ppm (Rudnev et al., 1979).

6. AQUATIC TOXICITY

6.1. ACUTE

A 7-day LC_{50} value of 97 mg/ℓ was determined for 1-chlorobutane in a static renewal assay with the guppy Poecilia reticulata (Könemann, 1981).

6.2. CHRONIC AND PLANT EFFECTS

Pertinent data regarding chronic toxicity and plant effects of monochlorobutanes were not located in the available literature.

6.3. RESIDUE

Specific information regarding residues of monochlorobutanes in aquatic organisms was not found in the available literature. Veith et al. (1980) have suggested, however, the use of the following equation to calculate BCFs:

$$\log BCF = 0.76 \log K_{ow} - 0.23,$$

where K_{ow} is the partition coefficient between octanol and water. Using this equation and the values log K_{ow} reported in Section 1, the BCF for whole fish was calculated to be within the range of 36-53.

6.5. OTHER RELEVANT INFORMATION

Other relevant information regarding monochlorobutanes was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Ambient or occupational exposure standards for monochlorobutanes were not located in the available literature.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic life were not encountered in the literature.

8. APPROACHES TO RISK ASSESSMENT

An approach for criteria derivation for the monochlorobutanes cannot be recommended due to the virtual lack or insufficiency of data regarding environmental fate, levels of exposures and biological effects.

Acute toxicity studies with 1- and 2-chlorobutane indicate a low order of oral, inhalation and dermal lethality for these compounds (Smyth et al., 1954, 1969; Rudnev et al., 1979), but information regarding the effects of subchronic exposure was inadequately reported in abstracts of Russian studies (Rudnev et al., 1979; Vinogradov, 1979), and is available only for 1-chlorobutane. Chronic toxicity studies have not been performed with 1-chlorobutane, 2-chlorobutane or t-butyl chloride.

All three of the monochlorobutanes have been tested for carcinogenic activity in the Strain A mouse lung tumor system, and increases in the number of pulmonary adenomas per mouse were associated with several of the administered doses of 2-chlorobutane and t-butyl chloride (Poirier et al., 1975). Dose-response relationships were not demonstrated, however, and the positive results may be regarded only as suggestive of carcinogenic activity. For the purpose of risk assessment, this assay system can only be used as a qualitative indication of potential carcinogenicity. Mutagenicity testing with 1-chlorobutane in two well-designed Ames assays was negative (Eder et al., 1980; Barber et al., 1981), and testing with 1-chlorobutane and t-butyl chloride in the pol A^- assay was inconclusive (Fluck et al., 1976). Oral administration of 1-chlorobutane to rats on days 1 through 19 of pregnancy at a level of 733 mg/kg/day reportedly caused embryotoxic and teratogenic effects (unspecified), but this information was published in an abstract of a Russian study and cannot be used for quantitative risk assessment.

9. REFERENCES

Barber, E.D. and W.H. Donish. 1982. An exposure system for quantitative measurements of the microbial mutagenicity of volatile liquids. Environ. Sci. Res. 25: 3-18.

Barber, E.D., W.H. Donish and K.R. Mueller. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. J. Mutat. Res. 90(1): 31-48

Briggs, G.C. 1981. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachlor. J. Agric. Food Chem. 29: 1050-1059.

Burns, L.H., D.M. Cline and R.R. Lassiter. 1981. Exposure Analysis Modeling System (EXAMS). Environmental Research Lab., ORD, U.S. EPA, Athens, GA.

Buswell, J.A. and P. Jurtschuk. 1969. Microbial oxidation of hydrocarbons measured by oxygraphy (using a Clark oxygen electrode). Arch. Mikrobiol. 64: 215-222.

Callahan, M.A., et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. 2. EPA 440/4-79-029b. Office of Water and Waste Management, U.S. EPA, Washington, DC.

CMR (Chemical Marketing Reporter). 1981. OPD Chemical Buyers' Directory Chemical Marketing Reporter. 69th annual ed. Schnell Publishing Co., Inc., New York, NY.

Eder, E., T. Neudecker, D. Lutz and D. Henschler. 1980. Mutagenic potential of alkyl and alkylic compounds: Structure-activity relationship as determined by alkylating and direct in vitro mutagenic properties. Biochem. Pharmacol. 29(7): 993-998.

Fluck, E.R., L.A. Poirier and H.W. Ruelius. 1976. Evaluation of a DNA polymerase-deficient mutant of E. coli for the rapid detection of carcinogens. J. Chem. Biol. Interact. 15: 219-231.

Gerhold, R.M. and G.W. Malaney. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. J. Water Pollut. Control Fed. 38: 562-579.

Graedel, T.E. 1978. Chemical Compounds in the Atmosphere. Academic Press, New York, NY.

Hawley, G.G. 1977. The Condensed Chemical Dictionary. Ninth ed. Van Nostrand Reinhold Co., NY.

Hellman, T.M. and F.H. Small. 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. J. Air Pollut. Control Assoc. 24: 979-982.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. In: Aquatic Toxicology, ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Ed. Am. Soc. Test. Mater. p. 78-115.

Könemann, H. 1981. Quantitative structure-activity relationships (QSARs) in fish toxicity studies. Toxicology. 19(3): 209-221.

Koskikallio, J. 1967. Kinetics of the hydrolysis of alkyl halides in perchloric acid-water mixtures. Acta Chem. Scand. 21: 397-407.

Laughton, P.M. and R.E. Robertson. 1959. Solvolysis in hydrogen and deuterium oxide. III. Alkyl halides. Can. J. Chem. 37: 1491-1497.

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7: 383-415.

Mabey, W.R., et al. 1982. Estimate of data for chemicals on the list, "Constituents of Concern for Chlorinated Organic Listings." EPA Contract No. 63-03-2981, OHEA, U.S. EPA, Washington, DC.

Mackay, D. and P.J. Leinonen. 1975. Rate of evaporation of low solubility contaminants from water bodies to atmosphere. Environ. Science Technol. 9: 1178-80.

Marion, C.V. and G.W. Malaney. 1963. The oxidation of aliphatic compounds by Alcaligenes faecalis. J. Water Pollut. Control Fed. 35: 1269-1284.

Maronpot, R. 1982. Recent Experience with the Strain A Mouse Pulmonary Tumor Bioassay Model. Presented at the Symposium on the Application of Short-term Bioassays in the Analysis of Complex Environmental Mixtures. Sponsored by U.S. EPA. Chapel Hill, NC. January 25-27.

NTP (National Toxicology Program). 1982. Chemicals on standard protocol, management status (1/8/82). National Toxicology Program, Carcinogenesis Testing Program, Bethesda MD. (Available from: Technical Information Resources Branch, Carcinogenesis Testing Program, National Toxicology Program, Loundow Bldg., Rm. A306, Bethesda, MD)

Poirier, L.A., D.D. Stoner and M.B. Shimkin. 1975. Bioassay of alkyl halides and nucleotide base analogs by pulmonary tumor response in Strain A mice. J. Cancer Res. 35: 1411-1415.

Roland, M. 1928. No title provided. Bull. Soc. Chim. Belg. 37: 117. (Cited in Mabey et al., 1982)

Rudnev, M.L., L.A. Tomashevskaya, G.I. Vinogradov, A.A. Kapustin, Z.I. Zholdakova and G.I. Leonskaya. 1979. Hygienic substantiation of the permissible content of benzyl and buytl chlorides in reservoir water. J. Gig. Sanit. 3: 11-15. (Cited in Chem. Abstr. 90: 19854a, 1979)

Schwarzenbach, R.P. and J. Westall. 1981. Transport of non-polar organic compounds from surface water to groundwater: Laboratory sorption studies. Environ. Science Technol. 15: 1360-67.

Shimkin, M.B. and G.D. Stoner. 1975. Lung tumors in mice: Application to carcinogenesis bioassay. J. Adv. Cancer Res. 21: 1-58.

Smyth, H.F., C.P. Carpenter, C.S. Weil and U.C. Pozzani. 1954. Range-finding toxicity data: List V. Am. Med. Assoc. Arch. Ind. Hyg. Occup. Med. 10: 61.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J. Striegel and J. Nycum. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30: 470.

SRI (Stanford Research Institute). 1981. 1981 Directory of Chemical Producers. SRI International, Menlo Park, CA.

Veith, G.D., K.J. Macek, S.R. Petrocelli and J. Carroll. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. In: Aquatic Toxicology, ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Ed. Am. Soc. Test. Mater. p. 116-129.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Co., NY.

Vinogradov, G.I. 1979. Autosensitizing effect in the per os administration of chemical substances to animals. 9: 100-102. (Cited in Chem. Abstr. 91: 205308g, 1979)

Weast, R.C., Ed. 1973. CRC Handbook of Chemistry and Physics. CRC Press, Inc., Boca Raton, FL. (Cited in Mabey et al., 1982)

Weast, R.C., Ed. 1980. CRC Handbook of Chemistry and Physics. CRC Press, Inc., Boca Raton, FL.

Williams, I.H. 1965. Gas chromatographic techniques for the identification of low concentrations of atmosphere pollutants. Anal. Chem. 37: 1117-1120.

Windholz, M., Ed. 1976. Merck Index. Ninth ed. Merck and Co., Inc., Rahway, NJ.

Wright, W.H. and J.M. Schaffer. 1932. Critical anthelmintic tests of chlorinated alkyl hydrocarbons and a correlation between the anthelmintic efficacy, chemical structure and physical properties. J. Am. Hyg. 16: 325-428.